Aberrant Semantic Activation in Schizophrenia: A Neurophysiological Study

Paul G. Nestor, Ph.D., Matthew O. Kimble, Ph.D., Brian F. O'Donnell, Ph.D., Lloyd Smith, M.S., Margaret Niznikiewicz, Ph.D., Martha E. Shenton, Ph.D., and Robert W. McCarley, M.D.

Objective: Schizophrenia has long been thought to be characterized by a fundamental disturbance in semantic associations, which has often been presumed to be of neurobiological origin. The authors examined the neurophysiological characteristics of semantic processing in schizophrenic patients. Method: During EEG recording, 15 schizophrenic patients and 15 age-matched comparison subjects read sentences that had either sensible or nonsensical endings. The authors recorded the N400 component, a specific negative event-related brain potential occurring approximately 400 msec after the final word in the sentence. N400 is highly, if not uniquely, sensitive to semantic expectancy and context, and larger, more negative N400 amplitude is associated with increased semantic unexpectancy. Results: In relation to the normal comparison subjects, the schizophrenic patients demonstrated prolonged N400 latency after nonsensical sentence endings and also showed enhanced N400 negativity, regardless of the sense of the sentence ending. Conclusions: These findings suggest slower and more diffuse semantic activation in patients with schizophrenia, perhaps reflective of a disease-related failure to maintain and to use semantic context.

(Am J Psychiatry 1997; 154:640–646)

Bleuler (1) first described schizophrenic thought in terms of a fundamental and primary disturbance of associations, perhaps best illustrated by his now famous example of his patient identifying members of her family as "mother, father, son, and Holy Ghost." Believing that these disturbed associations reflected disease-related organic pathology, Bleuler paved the way for more contemporary formulations that view semantic aberration as a cardinal feature of the schizophrenic genotype, often referred to as "schizotaxia" (2).

In support of Bleuler's observations, experimental studies have revealed that schizophrenic patients generate deviant, but not entirely bizarre, word associations that are similar to those produced by normal subjects when asked to free associate, that is, to refrain from goal-directed discourse (3). Under these conditions, normal subjects produce an abundance of strong word associations, such as "gold—fish," which are similar to the type of associative intrusions evident in schizophrenic discourse. In fact, experimental studies have shown that patients with schizophrenia often respond with the most dominant meaning or association (e.g., "pen" as a writing instrument) even when the context requires a less dominant or subordinate association or meaning (e.g., "pen" as a fenced enclosure) (3). Further studies have suggested that patients do not lack access to subordinate associations but may have difficulties using contextual influences to inhibit dominant but incorrect associations (3).

How might these semantic aberrations be represented in terms of brain activity? The human brain continuously produces electrical activity associated with current flowing across neuronal membranes. Some of the electrical currents are conducted to the scalp and recorded as EEG activity. Repeated stimulation of sensory receptors by visual, auditory, or somatosensory stimuli produces neural activity, often with time-locked positive and negative EEG deflections, which are known as event-related potentials. Computed by averaging EEG recordings over trials, an event-related potential is typically decomposed into specific, robust peaks, deflections, or components, which are named according to their latency—the time in milliseconds it

Received April 24, 1996; revision received Oct. 3, 1996; accepted Oct. 15, 1996. From the Department of Psychiatry, Harvard Medical School, Boston; the Department of Psychiatry, Brockton VA Medical Center; and the Department of Psychology, University of Massachusetts, Boston. Address reprint requests to Dr. McCarley, Department of Psychiatry, 116A, VA Medical Center, Brockton, MA 02401; mccarley@warren.med.harvard.edu (e-mail).

Supported by the Medical Research Service and the Schizophrenia Center of the Department of Veterans Affairs, NIMH grant MH-40779 to Dr. McCarley, NIMH grant MH-74605 to Dr. Shenton, and a Young Investigator Award to Dr. O'Donnell from the National Alliance for Research on Schizophrenia and Depression.

takes a peak to appear in the event-related potential after stimulus onset. Specific peaks may be characterized in terms of both amplitude, as measured in microvolts, and latency, as indicated in milliseconds. Neither of these measurements requires a behavioral response, and they therefore may be viewed as real-time probes of both neuronal activity and information processing.

One particularly interesting component of event-related potentials is the N400, a negative potential occurring approximately 400 msec poststimulus, elicited by semantically anomalous or unexpected words in a sentence (4). Highly, if not uniquely, sensitive to semantic expectancy or context (4–6), N400 amplitude is enhanced by nonsensical sentence endings (e.g., "People pray in their local nest") but not by sensible sentence endings (e.g., "People pray in their local church") and by unrelated word pairs (e.g., doctor—bread) but not by related word pairs (e.g., doctor—nurse). N400 is not elicited by unexpected musical notes in a melody sequence, unexpected shapes in a series of shapes, unexpected numbers in a numeric series, or unexpected letters in an alphabet sequence (7, 8). Occurring in the absence of a behavioral response, the N400 is typically followed by a late positive component, approximately 500–700 msec poststimulus, known as the P600. Although the functional significance of the P600 has yet to be elucidated, it is thought to be related to a more general process of attention and decision making (9).

While only a relatively small number of N400 studies of schizophrenic patients have been performed (10–13), these investigations have shown a disease-related delay in N400 latency, suggestive of slow semantic processing. Differences in N400 amplitude between schizophrenic and comparison subjects have been also demonstrated but are less robust, limited to paradigms using sentences (12, 13). In these studies and in studies of normal subjects, N400 amplitude is conventionally measured as a difference waveform, computed by subtracting the N400 amplitude for sensible sentences from that for nonsensical sentences. Using difference waveforms, we, for example, found lower N400 amplitudes in patients with chronic schizophrenia than in normal subjects, which we interpreted as evidence of a deficit in semantic congruence in patients with schizophrenia (12).

Use of N400 difference waveforms is based on the assumption that comparison subjects and patients show similar amplitudes for sensible sentences. For normal subjects, N400 amplitude decreases across word position for sensible sentences, with the last word of a sensible sentence eliciting very small N400 amplitudes (14–16). The increasing contextual influence of words in the semantic processing of sensible sentences is thought to constrain N400 amplitude in normal subjects. By contrast, patients with schizophrenia may fail to use context appropriately (17), and N400 abnormalities may thus be evident for sensible sentences as well as for nonsensical sentences. These abnormalities, coupled with prolonged N400 latency, may reflect abnormal semantic activation that presumably contributes to associative intrusions in schizophrenic discourse.

Previous studies with schizophrenic patients have examined N400 primarily in terms of difference waveforms (12, 13), and in so doing they have not distinguished a general loss of context from a specific insensitivity to semantic incongruence. The former may be operationalized in terms of N400 amplitude for sensible sentences, and the latter may be measured in terms of the N400 amplitude difference waveform. Thus, in the present study, we again recorded N400 for the last words of 40 sensible sentences and 40 nonsensical sentences in patients with schizophrenia and age-matched comparison subjects. We analyzed N400 in terms of three distinct aspects of semantic processing: 1) semantic processing speed, as reflected by N400 latency; 2) semantic congruency, as reflected by N400 difference waveforms (amplitude); and 3) semantic context, as reflected by N400 amplitude for sensible sentences.

METHOD

Subjects

Fifteen chronically ill, right-handed male schizophrenic patients and 15 right-handed normal comparison subjects participated in the study. All subjects provided written informed consent. All subjects were between the ages of 20 and 55 years, native speakers of English, and without histories of ECT, neurological illness, or DSM-III-R diagnosis of drug or alcohol abuse. No subjects were taking medications that would grossly affect the EEG (e.g., reserpine or barbiturates). The DSM-III-R diagnosis was ascertained on the basis of a structured psychiatric interview, the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (18), and medical chart review. All patients were receiving neuroleptic medication at a mean daily dose equivalent to 455 mg of chlorpromazine (SD=308). The mean duration of illness was 17.3 years (SD=7.1). The patients had been hospitalized 27.3% of the time since the first episode on average. The patients scored in the low average range on selective subtests of the Wechsler Adult Intelligence Scale—Revised (WAIS-R) (19), with the exception of a mean score in the average range on the information subtest. The mean scores also fell in the low average range on tests of verbal and visual memory from the Wechsler Memory Scale—Revised (20) but in the impaired range for number of categories achieved on the Wisconsin Card Sorting Test (21).

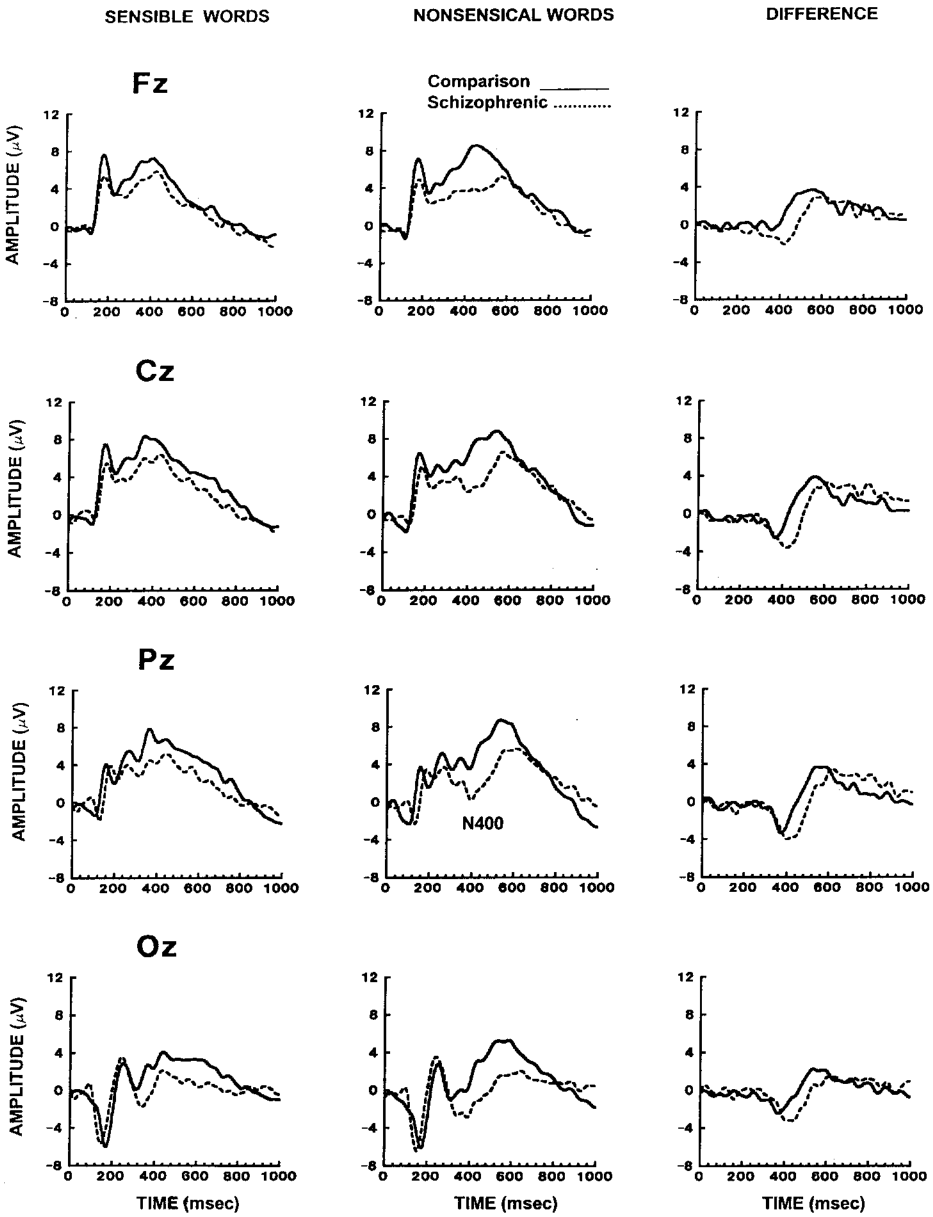
Comparison subjects were recruited from newspaper advertisements and were matched to the patients on the basis of age, sex, and handedness. A potential comparison subject was excluded if he had a personal or family history of mental illness. Mean age did not differ between the comparison subjects (mean=35.9 years, SD=7.2) and the patients (mean=37.9 years, SD=7.6). There was also no difference between mean scores on the information subscale of the WAIS-R for the comparison subjects (mean=10.8, SD=2.9) and schizophrenic patients (mean=10.2, SD=3.1).

Event-Related Potentials Evaluation

The sentences were directly adapted from those of Kutas et al. (9) and identical to those used in our previous study (12). A total of 80 sentences were used. One-half of the sentences had final words that were highly constrained by the preceding sentence context (cloze probability, >0.85; sensible), and one-half did not (cloze probability, <0.01; nonsensical). Individual words were sequentially presented on a video monitor, and the subjects were seated approximately 1 m from the screen (stimuli subtended 1° of visual angle). Event-related potentials were collected only after the final word of each sentence.

The experimental task was automatically presented. Each word of

FIGURE 1. Event-Related Potentials at Central Electrode Sites for Sensible and Nonsensical Sentence Endings Presented to 15 Normal Subjects and 15 Schizophrenic Patients[a]



[a]Nonsensical sentence endings elicit the N400 deflection at about 400 msec, followed by a broad positive deflection peaking at about 600 msec. The difference waveform, generated by subtraction of the event-related potential for sensible words from that for nonsensical words, isolates the N400 and P600 components.

the sentence was displayed for 250 msec, with an interword interval of 1 sec and an intersentence interval of 4 sec. The final word was followed by a period, which prompted a response. The subjects were instructed to indicate the sensibility of the sentence. A "yes" response indicated the sentence made sense, and "no" signified that the sentence was nonsensical. The subjects responded by pressing the left button for "yes" and the right button for "no" (counterbalanced between subjects). The responses were monitored by an assistant who sat behind the subject. A total of 80 sentences were presented (40 sensible, 40 nonsensical).

Event-related potentials were recorded from 28 tin-plate electrodes referred to linked ears by using an electrode cap (Electro-Cap International, Inc., Eaton, Ohio). The scalp electrode placements included all electrodes in the International 10-20 system with eight additional interpolated electrodes. The Fp1, Fp2, and Cz sites were located by precise International 10-20 measurements, and all other electrodes were positioned automatically at standard relative distances. A vertical electro-oculogram (EOG) was recorded by using right eye supra- and infraorbital electrodes. Horizontal EOG was recorded from electrodes at the right and left external canthi. Electrode impedance was maintained at less than 4 kΩ. The EEG was filtered by using 0.15–40.00-Hz EEG amplifiers (NeuroScience, Inc., Milpitas, Calif.), with 36 dB/octave rolloff for low pass and 6 dB/octave for high pass. Single-trial epochs were digitized and stored on a computer hard disk for later off-line processing. Each event-related potential consisted of 256 EEG samples over a 1000-msec time epoch, including a 100-msec prestimulus baseline interval.

Data Processing and Analysis

All single-trial epochs were baseline corrected before processing. Event-related potentials with vertical EOG artifact were corrected through individually computed weighting coefficients at each electrode site (22). After correction for vertical EOG artifact, all epochs with voltages in excess of 50 or –50 μV at any site were rejected. The data were then averaged over the trials for the sensible and the nonsensical final words. N400 was measured from each subject's event-related potentials for sensible and nonsensical words and for the difference between the two waveforms (nonsensical minus sensible). N400 amplitude was measured as the mean voltage between 360 and 470 msec for sensible and nonsensical sentences, which captured the descending phase and nadir of the N400 in all subjects. Similarly, P600 amplitude was measured as the mean voltage between 550 and 650 msec. N400 peak component latency was defined as the data point at each of the central and lateral electrodes with the largest negative voltage between 360 and 470 msec. P600 peak component latency was defined as the data point at each of the central and lateral electrode sites with the largest positive voltage between 550 and 650 msec.

Two separate repeated measures analyses of variance (ANOVAs) were performed on area N400 amplitude measures, one for central electrode sites (Fz, Cz, Pz, Oz) and one for lateral or coronal sites (T3, T5, T4, T6) (23). To isolate further the effect of sentence reading on N400, repeated measures ANOVAs were also used to analyze group differences in N400 amplitude as a function of sentence type and electrode site. Repeated measures ANOVAs were used to examine N400 difference waveforms as a function of electrode site. P600 waveforms were similarly analyzed.

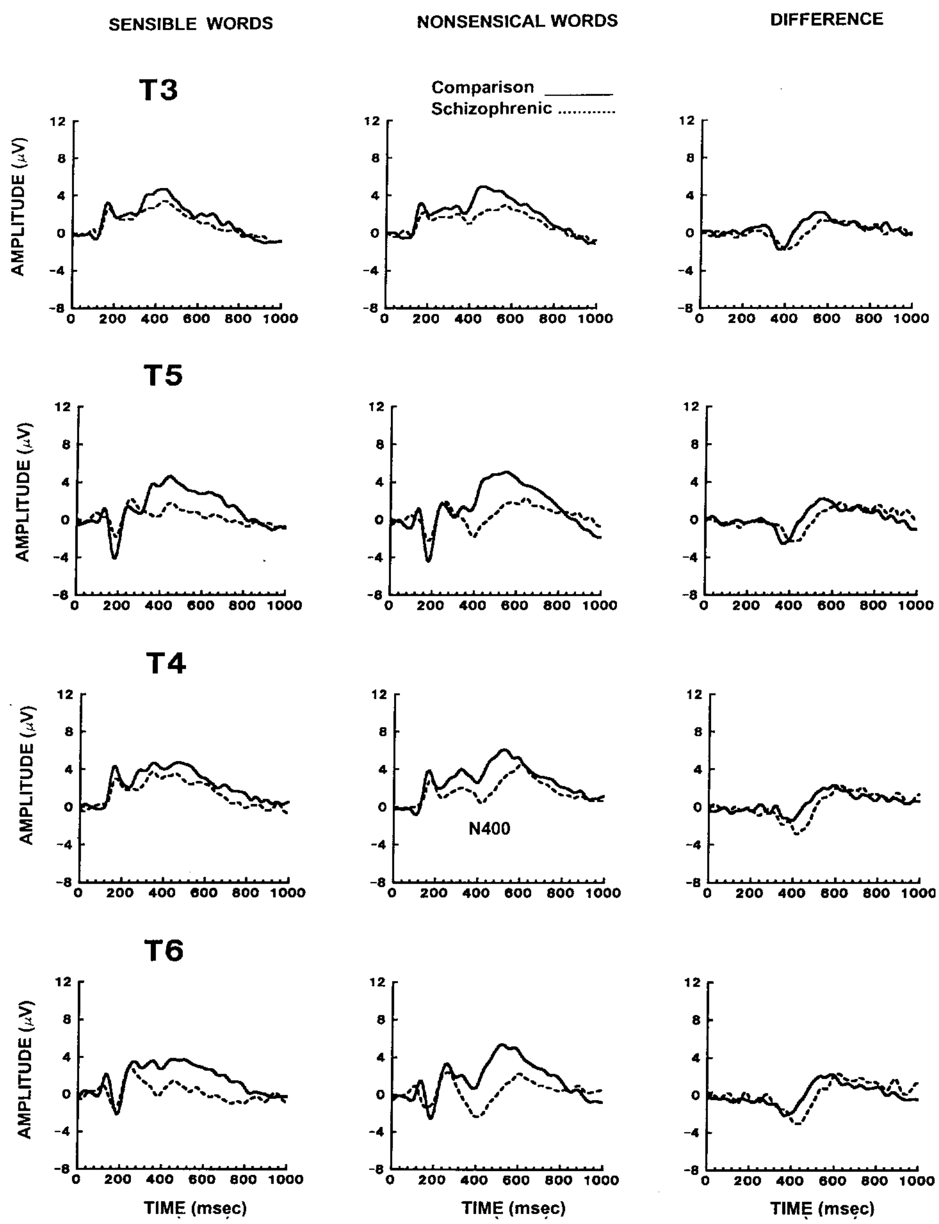
RESULTS

The grand averaged N400 waveforms are shown in figure 1 and figure 2. Figure 1 shows N400 from central electrode sites, and figure 2 presents N400 from lateral electrode sites.

Amplitude

Table 1 presents mean amplitude as a function of electrode site for both groups and for both sensible and nonsensical sentences. N400 area measures were first examined as a function of sentence type for both groups. A repeated measures ANOVA with one between-group factor (schizophrenic versus comparison subjects) and two repeated factors of central electrode sites (Fz, Cz, Pz, Oz) and sentence type (sensible versus nonsensical) revealed significant effects for group ($F=4.17$, $df=1, 28$, $p=0.05$) and sentence type ($F=40.43$, $df=1, 28$, $p<0.001$) and a nearly significant effect for the interaction of group and sentence type ($F=3.92$, $df=1, 28$, $p< 0.06$). Figure 1 reveals that in relation to the comparison subjects, the schizophrenic patients had greater N400 negativity (downward deflection) at the central electrode sites, particularly for the nonsensical sentences. For the lateral electrode sites (T3, T5, T4, T6), ANOVA revealed significant effects for group ($F=6.70$, $df=1, 28$, $p<0.01$) and sentence type ($F=68.66$, $df=1, 28$, $p<0.001$) but no significant effect for the interaction of group and sentence type. As figure 2 shows, in relation to the comparison subjects, the schizophrenic patients had greater negativity at the lateral electrode sites regardless of sentence type.

FIGURE 2. Event-Related Potentials at Lateral Electrode Sites Overlying the Temporal Region of the Brain for Sensible and Nonsensical Sentence Endings Presented to 15 Normal Subjects and 15 Schizophrenic Patients[a]



[a]Nonsensical sentence endings elicit the N400 deflection at about 400 msec, followed by a broad positive deflection peaking at about 600 msec. The difference waveform, generated by subtraction of the event-related potential for sensible words from that for nonsensical words, isolates the N400 and P600 components.

These analyses indicated significant group differences in N400 amplitude for both sensible and nonsensical sentences. As revealed in figures 1 and 2, the patients with schizophrenia showed significantly greater negativity for the presumably baseline, sensible sentences and for the experimental, nonsensical sentences. The N400 difference waveforms, also presented in both figures 1 and 2, thus reflected these group amplitude differences for both conditions. These N400 difference waveforms were computed and submitted to a repeated measures ANOVA with one between-group factor (schizophrenic versus comparison subjects) and one repeated factor of central electrode sites (Fz, Cz, Pz, Oz). ANOVA revealed no significant effect for group, for central electrode sites, or for

TABLE 1. Amplitude of N400 EEG Component for Sensible and Nonsensical Sentence Endings Presented to 15 Normal Subjects and 15 Schizophrenic Patients

	Amplitude (μV)							
	Normal Subjects				Schizophrenic Patients			
	Sensible		Nonsensical		Sensible		Nonsensical	
Electrode	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Fz	6.84	5.20	7.01	5.35	5.29	2.91	3.69	3.27
Cz	7.56	5.30	6.07	5.71	5.89	3.10	2.54	3.31
Pz	6.67	4.49	4.05	5.13	4.69	3.37	0.61	3.49
Oz	3.08	4.12	0.50	4.67	1.09	3.10	–2.29	3.54
T3	4.45	2.62	2.72	2.50	3.05	1.71	1.24	2.13
T5	3.95	3.44	1.48	4.13	1.07	2.00	–1.46	2.97
T4	4.47	2.90	2.85	3.30	3.29	2.22	0.97	2.02
T6	3.27	3.44	0.95	4.32	0.68	2.60	–2.21	2.46

the interaction between group and central electrode sites. Similarly, ANOVA revealed no significant effects for N400 difference waveforms for the lateral sites (T3, T5, T4, T6). Thus, these analyses of N400 difference waveforms suggested that the schizophrenic patients did not differ significantly from the comparison subjects on this measure of semantic congruence.

As also presented in figures 1 and 2, the schizophrenic patients showed greater negativity for the P600 component. Indeed, for the central electrode sites (Oz, Pz, Cz, Fz), ANOVA revealed a significant group effect ($F=7.09$, $df=1, 28$, $p<0.05$) but no significant effect for the interaction of group and sentence type. Similarly, for the lateral electrode sites (T3, T5, T4, T6), ANOVA revealed a highly significant group effect ($F=11.20$, $df=1, 28$, $p<0.01$) but no significant effect for the interaction of group and sentence type.

To test for group differences in N400 topography, N400 area measures were assessed for the central (Fz, Cz, Pz, Oz) and lateral (T3, T5, T4, T6) electrodes. ANOVAs revealed no significant interaction between group and electrode site for either the N400 difference waveform or the N400 measured from sensible and nonsensical waveforms. These analyses indicated similar N400 topographies for the schizophrenic and comparison groups, as evidenced by the absence of a significant interaction between electrode site and group. Similarly, for P600 the two groups showed similar topographical distributions for the central (Fz, Cz, Pz, Oz) and lateral (T3, T5, T4, T6) sites.

Latency

The N400 component latency at peak amplitude was computed for the nonsensical sentences at both the central and lateral electrode sites. For the central electrode sites (Fz, Cz, Pz, Oz), a repeated measures ANOVA revealed only a significant group effect ($F=7.35$, $df=1, 28$, $p<0.01$). In relation to the normal comparison subjects, the schizophrenic patients showed an average 24-msec longer N400 latency across the central electrode sites. For example, for central electrode site Cz, the mean N400 peak latency was 384 msec ($SD=30$) for the comparison subjects and 411 msec ($SD=32$) for the schizophrenic patients. For the lateral electrode sites (T3, T5, T4, T6), a repeated measure ANOVA revealed significant effects for group ($F=11.29$, $df=1, 28$, $p<0.01$) and electrode site ($F=3.22$, $df=3, 26$, $p<0.05$). In relation to the normal comparison subjects, the schizophrenic patients showed an average 25-msec longer N400 latency across the lateral electrode sites. Both groups had their slowest N400 at lateral electrode site T4, with mean N400 latencies of 393 msec ($SD=35$) and 417 msec ($SD=29$) for the comparison and schizophrenic groups, respectively. For the P600 peak latency, ANOVAs also revealed significant group effects for both central ($F=12.04$, $df=1, 28$, $p<0.01$) and lateral ($F=9.02$, $df=1, 28$, $p<0.01$) sites, with the schizophrenic patients showing significantly longer P600 latency.

Accuracy

Because of technical problems, accuracy measures were available for only nine patients and 13 comparison subjects. Both groups showed relatively high levels of accuracy. The mean accuracy was 98% (SD=2%) for the comparison subjects and 94% (SD=6%) for the schizophrenic patients. A t test revealed a significant difference between groups ($t=2.29$, $df=20$, $p<0.05$).

DISCUSSION

The current study used an N400 sentence paradigm to examine the influence of semantic context on neurophysiological activity in both schizophrenic patients and age-matched comparison subjects. In relation to the normal comparison subjects, the schizophrenic patients had longer N400 latencies, suggestive of a disease-related slowing in semantic processing. Similarly, the schizophrenic patients also showed greater negativity in N400 amplitude for sentence endings, regardless of whether these endings were sensible or nonsensical. This finding suggests that neurophysiological activity may indeed be less constrained by semantic context in schizophrenic patients than in comparison subjects. By contrast, N400 difference waveforms did not separate the schizophrenic patients from the comparison subjects; both groups showed more negativity for nonsensical sentences than for sensible sentences. Thus, while less influenced by the general semantic context of sentences, N400 in the schizophrenic patients did not show an insensitivity to incongruence.

The most robust N400 finding for the schizophrenic patients was the prolonged latency. In the present experiment the patients had, on average, a 24-msec longer N400 latency than did the normal comparison subjects, which was consistent with the findings of our previous study (12). While a general slowing in behavioral response typically characterizes schizophrenic patients (24) and patients with a variety of other psychiatric and neurological disorders (25), the N400 latency measure, unlike behavioral response times, is not dependent on motor responses or other peripheral factors that are known to slow reaction time. In addition, studies of other brain potential components do not always show prolonged latency in schizophrenic patients (26).

N400 slowing in schizophrenic patients may thus be specific to the cognitive and neural computations involved in the semantic processing of sentences. It may correspond to the slowness of thought, often referred to as "bradyphrenia," commonly observed in patients with chronic schizophrenia. Prolonged N400 latency may mean that the speed of firing of neuronal elements in response to read words is considerably slower in patients with schizophrenia.

It may also indicate an abnormal spread of neuronal activation, as reflected by the overall enhanced N400 negativity in patients with schizophrenia. The spread of activation may be more diffuse, as suggested by the Meehl model of hypokrisia (2). From this vantage point, because activation may cover greater neural space, N400 latency is prolonged in patients with schizophrenia.

In our previous study (12), schizophrenic patients showed smaller N400 difference waveforms than did comparison subjects, which we interpreted as evidence of a disease-related insensitivity to incongruence. In the present study, N400 difference waveforms did not distinguish schizophrenic patients from normal comparison subjects, suggesting that the patients did not show an insensitivity to incongruity. One principal difference between these studies is that in the previous study we relied exclusively on N400 difference waveforms, as is conventional in N400 studies, and did not measure N400 amplitude as a function of sensible and nonsensical conditions alone. However, we could not rely on difference waveforms in the present study because the patients differed from the comparison subjects in the sensible, presumably baseline condition. Similarly, it cannot be ruled out that in our previous study the abnormalities in N400 difference waveforms for the schizophrenic patients reflected abnormalities in their responses to the sentences with sensible final words rather than those with nonsensical endings. By examining N400 in terms of both difference waveforms and sentence type in the current study, we sought to distinguish abnormalities due to an insensitivity to incongruence from those due to a failure to use general semantic context. Given the overall observed difference in N400 amplitude regardless of sentence type, the data suggest abnormalities in using general semantic context rather than a more specific insensitivity to incongruity.

The failure to find a disease-related insensitivity to incongruence did not appear to be due to a weak experimental effect. Both groups showed greater negativity for nonsensical sentences than for sensible sentences, and ANOVAs consistently revealed a highly statistically significant effect for sentence type. However, the sentence paradigm used in this study was originally normed for children, and the overall probability of a nonsensical sentence ending was relatively high (0.5). The limited difficulty of the task and the relatively high probability of nonsensical sentences may have lessened the semantic incongruity effect, especially for the comparison subjects. For example, the comparison subjects may have come to expect nonsensical sentence endings given the overall context and thus may not have shown a pronounced incongruence effect.

These considerations are supported by studies that have suggested that N400 amplitude may be related more to semantic expectancy, operationalized in terms of cloze probability, than to semantic incongruency; that is, unexpected but semantically congruent sentence endings elicit N400 waveforms in healthy subjects (see, for instance, references 4–6). Thus, in relation to normal comparison subjects, patients with schizophrenia may have more difficulties using context to generate expectancies. N400 amplitude may be also related to the degree of association among words (27) or their conceptual representations (28). Conceptual representations and associations may be primed or constrained by the preceding context. Recall that for normal comparison subjects N400 amplitude decreases across word position in sensible sentences presumably because of contextual constraints (14–16). In schizophrenic patients, greater negativity and longer N400 latency may therefore suggest an overactivation of conceptual nodes due to a working memory failure to maintain preceding contextually constraining information.

The precise neurobiological mechanisms underlying these N400 abnormalities in schizophrenia are unknown, although several distinct but not necessarily competing theoretical models may be useful to consider. For example, if these N400 abnormalities are related to a working memory failure, then a dopaminergically modulated prefrontal disturbance may be implicated (17). On the other hand, N400 abnormalities in schizophrenic patients may be related to the specific semantic, linguistic content of the task. As support for this hypothesis, the schizophrenic and comparison subjects in this study showed similar amplitudes for early component waveforms (e.g., P200), which are typically considered to be more sensitive to general attentional and perceptual processes than to specific linguistic operations. Later components, specifically the linguistically sensitive N400 component, separated the schizophrenic patients from the comparison subjects. These subsequent N400 abnormalities may represent disease-related semantic anomalies and may be viewed as consistent with the hypothesis of left temporal lobe involvement in patients with schizophrenia (29, 30). However, the schizophrenic patients and comparison subjects also showed amplitude differences in P600. This later potential may be more related to general attentional processes than to specific linguistic operations (9).

In summary, further experiments need to be performed to compare the N400 disturbance in schizophrenic patients with their other abnormalities in event-related potentials, most notably P300 abnormalities, which are often influenced by stimulus predictability but are not thought to index conceptual knowledge. Similarly, there is a need for additional experiments that will combine N400 with well-designed semantic priming paradigms that have provided behavioral evidence of heightened semantic activation in patients with schizophrenia; the study by Kwapil et al. (31) is one such study. Such experiments may help further elucidate the functional significance of N400 abnormalities in patients with schizophrenia.

REFERENCES

1. Bleuler E: Dementia Praecox or the Group of Schizophrenias (1911). Translated by Zinkin J. New York, International Universities Press, 1950
2. Meehl PE: Schizotaxia revisited. Arch Gen Psychiatry 1989; 46: 935–944
3. Chapman LJ, Chapman JP: Disordered Thought in Schizophrenia. Englewood Cliffs, NJ, Prentice-Hall, 1973
4. Kutas M, Hillyard SA: Reading senseless sentences: brain potentials reflect semantic incongruity. Science 1980; 207:203–205
5. Fischler I, Bloom PA, Childers DG, Roucos SE, Perry NW: Brain potentials related to stages of sentence verification. Psychophysiology 1983; 20:400–409
6. Fischler I, Bloom PA, Childers DG, Arroyo AA, Perry NW: Brain potentials during sentence verification: late negativity and long term memory strength. Neuropsychologia 1984; 22:559–568
7. Besson M, Macari F: An event-related potential analysis of incongruity in music and other non-linguistic contexts. Psychophysiology 1987; 24:14–25
8. Polich J: N400 from sentences, semantic categories, numbers, and letter strings? Bull Psychonomic Soc 1985; 23:361–364
9. Kutas M, Neville HJ, Holcomb PJ: A preliminary comparison of the N400 response to semantic anomalies during reading, listening and signing. Electroencephalogr Clin Neurophysiol Suppl 1987; 39:325–330
10. Grillon C, Ameli R, Glazer WM: N400 and semantic categorization in schizophrenia. Biol Psychiatry 1991; 29:467–480
11. Koyama S, Nageishi Y, Shimokochi M, Hokama H, Miyazato Y, Miyatani M, Ogura C: The N400 component of event-related potentials in schizophrenic patients: a preliminary study. Electroencephalogr Clin Neurophysiol 1991; 78:124–132
12. Adams J, Faux SF, Nestor PG, Shenton M, Marcy B, Smith S, McCarley RW: ERP abnormalities during semantic processing in schizophrenia. Schizophr Res 1993; 10:247–257
13. Mitchell PF, Andrews S, Fox AM, Catts SV, Ward PB, McConaghy N: Active and passive attention in schizophrenia: an ERP study of information processing in a linguistic task. Biol Psychol 1991; 32:101–124
14. Kutas M, Van Petten C, Besson M: Event-related potential asymmetries during the reading of sentences. Electroencephalogr Clin Neurophysiol 1988; 69:218–233
15. Van Petten C, Kutas M: Interactions between sentence context and word frequency in event-related potentials. Memory & Cognition 1990; 18:380–393
16. Van Petten C, Kutas M: Influences of semantic and syntactic context on open- and closed-class words. Memory & Cognition 1991; 19:95–112
17. Cohen JD, Schreiber-Servan D: Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychol Rev 1992; 99:45–77
18. Spitzer RL, Endicott J: Schedule for Affective Disorders and Schizophrenia—Lifetime Version, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1978
19. Wechsler D: Wechsler Adult Intelligence Scale—Revised Manual. New York, Harcourt Brace Jovanovich, 1981
20. Wechsler D: Wechsler Memory Scale—Revised Manual. New York, Harcourt Brace Jovanovich, 1987
21. Heaton RK: The Wisconsin Card Sorting Test Manual. Odessa, Fla, Psychological Assessment Resources, 1981
22. Semlitsch H, Anderer P, Schuster P, Presslich O: A solution for reliable and valid reduction of ocular artifacts applied to the P300 ERP. Psychophysiol 1986; 23:695–703
23. Niznikiewicz M, O'Donnell BF, Nestor PG, Smith L, Law S, Karapelou ME, Shenton M, McCarley RW: ERP assessment of visual and auditory language processing in schizophrenia. J Abnorm Psychol 1997; 106:1–10
24. Nuechterlein KH: Reaction time and attention in schizophrenia: a critical evaluation of the data and theories. Schizophr Bull 1977; 3:373–428
25. Benton AL: Reaction time in brain disease: some reflections. Cortex 1986; 22:129–140
26. O'Donnell BF, Shenton ME, McCarley RW, Faux SF, Smith RS, Salisbury DF, Nestor PG, Pollak SD, Kikinis R, Jolesz FA: The auditory N2 component in schizophrenia: relationship to MRI temporal lobe gray matter and to other ERP abnormalities. Biol Psychiatry 1993; 34:26–40
27. Bentin S, McCarthy G, Wood CC: Event-related potentials associated with semantic priming. Electroencephalogr Clin Neurophysiol 1985; 60:343–355
28. Nigam A, Hoffman JE, Simons RF: N400 to semantically anomalous pictures and words. J Cognitive Neuroscience 1992; 4:15–22
29. Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, Hokama H, Martin J, Metcalf D, Coleman M, McCarley RW: Abnormalities of the left temporal lobe and thought disorder in schizophrenia: a quantitative magnetic resonance imaging study. N Engl J Med 1992; 327:604–612
30. Nestor PG, Shenton ME, McCarley RW, Haimson J, Smith RS, O'Donnell B, Kimble M, Kikinis R, Jolesz FA: Neuropsychological correlates of MRI temporal lobe abnormalities in schizophrenia. Am J Psychiatry 1993; 150:1849–1855
31. Kwapil TR, Hegley DC, Chapman LJ, Chapman JP: Facilitation of word recognition by semantic priming in schizophrenia. J Abnorm Psychol 1990; 99:215–221